REMARKS

This document is filed responsive to the Office Action dated October 31, 2007. In that Action, Claims 1-4, 7-26, 31-34, 36, 37, 42, 51 and 53-64 were pending in the present application. Claims 31, 51, 53-56, 58 and 59 have been withdrawn from consideration as being drawn to a non-elected invention. Of the remaining pending claims, claims 1, 2, 4, 7-26, 32-34, 36, 37, 42, 57 and 60-64 have been rejected and claim 3 objected to by the Examiner in the instant Office Action.

In the instant Response, Applicants have amended claims 1, 3, 4, 34. Claim 10 has been canceled. New claims 65-70 have been added. Support for the amendments to claims 1 and 34 can be found on page 4, lines 12-13, page 5, lines 21-25, page 4, lines 4-8, original claim 10 and on page 7, lines 28-32. Support for new claims 65-68 can be found on page 23, lines 18-31. Support for new claim 69 can be found in original claim 10 and on page 7, lines 28-32. Support for new claim 70 can be found on page 26, lines 13-18.

Oath/Declaration

The Examiner states that the declaration filed in this case is defective and not in compliance with 37 CFR 1.67(a), as neither the application number nor the filing date appear on the executed declaration.

With respect to the Examiner's according non-compliant status for the Declaration of Paul Dunn for the reason that the Declaration of Paul Dunn does not identify the instant application or priority application for the instant application, Applicants note that according to PTO procedure, in response to such a notice, Applicants may request reconsideration of the Examiner's decision by filing supplemental evidence, according to MPEP 409.03.

Accordingly, Applicants submit a First Declaration of Robert Spavin under 37 CFR 1.132 providing such supplemental evidence. The First Declaration of Robert Spavin provides the attested statement of assignee Crusade Laboratories' legal counsel, Mr. Robert Spavin, setting forth the facts as they pertain to inventor Paul Dunn's signature on the allegedly non-compliant Declaration of Paul Dunn. Namely, Mr. Spavin represents that he witnessed Paul Dunn's signature on the alleged non-compliant Declaration of Paul Dunn, as well as an Assignment document (which has since been filed for the instant case), both on December 19, 2003. Mr.

Spavin states that he understood Mr. Dunn's intent to be to make the Declaration of Paul Dunn for the priority PCT application ((PCT/GB2004/004851) as well as a subsequent U.S. national phase application (i.e., the instant application). The Assignment is recorded at Reel 017898, Frame 0173. Copies of both the Assignment and the Declaration of Paul Dunn, both signed by Paul Dunn on December 19, 2003, are attached to the First Declaration of Robert Spavin.

Reconsideration is respectfully requested.

Specification

The Examiner contends that the title of the invention is not descriptive and required a new title that is clearly indicative of the invention to which the claims are directed. Responsive to this objection, Applicants have presented a new title, Mutant Herpes Simplex Viruses Comprising Nucleic Acid Encoding A Nitroreductase. Reconsideration is respectfully requested.

Claim Objections

The Examiner has objected to claims 3 and 4 for informality for reciting sequence identifier numbers in non-standard format. Responsive to this objection, Applicants have amended claims 3 and 4 according to the Examiner's suggestion. Reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claim 4 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Specifically, the Examiner contends that the genus of polypeptides having at least 60% or at least 70% identity with, or hybridizing under high stringency conditions to, SEQ ID NO:2 or to a nucleic acid encoding the polypeptide of SEQ ID NO:1, lacks sufficient recitation of distinguishing identifying characteristics to provide adequate written description of the genus to demonstrate that the inventors, at the time the invention was filed, had possession of the claimed invention.

Responsive to this rejection, Applicants have amended claim 4 to remove clauses (b) and (c) relating to recital of 70% identity and recital of hybridization language. Applicants have also amended the recital of sufficient sequence identity to 90%. The claim has also been amended to specify a function of the polypeptides (i.e., nitroreductase activity) encoded by the recited

sequences. According to the Revised Interim Written Description Guidelines Training Materials currently guiding Office Policy, the amendments to claim 4 reciting a significantly smaller genus of sequences, together with the recital of a function of the encoded polypeptides, should be sufficient to demonstrate the Applicants' possession of the claimed invention.

Reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claim 57 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. Specifically, the Examiner contends that the reference to the deposit of biological material in the specification does not include any indication of public availability.

Responsive to this rejection, Applicants provide the Second Declaration of Robert Spavin, legal counsel for Assignee Crusade Laboratories, Inc., stating that the above-referenced deposit was made under the terms of the Budapest Treaty and the subject of claim 57 and the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent.

Reconsideration is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 4 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends that the claim recites "high stringency conditions" but does not provide specific parameters of this term.

Responsive to this rejection, Applicants have canceled language in the claim making reference to "high stringency conditions," thereby mooting the rejection. Reconsideration is respectfully requested.

Rejection under 35 USC § 102(b)

Claims 1, 2, 4, 7-16, 32-34, 60 and 61 have been rejected under 35 USC § 102(b) as allegedly being anticipated by Coffin et al. (WO 99/38955) as evidenced by Anlezark et al. (WO

93/08288). Specifically, the Examiner contends that WO 99/38955 discloses HSV comprising a heterologous gene which can be *E. coli* nitroreductase.

Responsive to this rejection, claims 1 and 34 are amended to limit the recited HSV to those that are oncolytic, that do not produce a functional ICP34.5 gene product, and that are mutants of one of HSV-1 strains 17 or F or HSV-2 strain HG52. New claims 65-68 limit the herpes simplex virus genome to a genome that substantially resembles, or is, the genome of HSV-1 strain 17 or F or HSV-2 strain HG52. Claims 67 and 68 also specify that the genome has a mutation in the ribonucleotide reductase gene.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). It is respectfully submitted that, for example, the limitation requiring that the HSV be oncolytic, distinguishes the instant claim from Coffin et al. Specifically, Coffin et al. relates to the use of non-pathogenic HSV as vectors in methods of gene therapy (page 1, lines 5-8). In particular, Coffin et al. requires that these HSV lack a functional ICP4 gene (see page 2, lines 29-31 and the claims), i.e. it has an inactivating mutation in ICP4 (page 2, lines 21-22). Page 1, lines 22-23, states that a virus lacking ICP4 cannot grow lytically, i.e. it is not (and cannot be) oncolytic. Thus, the HSV disclosed in Coffin et al. are not oncolytic.

Applicants note that Coffin et al. is concerned with the use of HSV as a vector for gene therapy. Page 1, lines 16-18 of WO 99/38955 states that "use of HSV as a vector requires the development of strains carrying mutations that disrupt the lytic cycle...". In other words, WO 99/38955 teaches that use of HSV as a vector for gene therapy requires that the HSV is not oncolytic. The HSV disclosed in Coffin et al. carry a mutation in the ICP4 gene (page 2, lines 29-31 and the claims), which are not oncolytic (page 1 lines 22-23).

That Coffin et al. does not teach the use of HSV to lyse cells is borne out by the Examples. These assess the toxicity of various HSV mutants by infecting cells with the mutants and observing cell viability after time intervals up to one month. Examples 2 and 4 only relate to HSV mutants that contain the ICP4 mutation. Although Example 3 tests some HSV mutants that do not contain the ICP4 mutation, this is merely to illustrate the "considerably reduced toxicity" of a HSV mutant containing the ICP4 mutation and other mutations. Example 1 describes construction of the HSV mutants.

It is respectfully submitted that the teachings of the reference do not teach an oncolytic HSV, and therefore, not all elements present in the instant claims are taught by Coffin et al.

Reconsideration is respectfully requested.

Rejections under 35 USC § 103(a)

Claims 17-26

Claims 17-26 have been rejected under 35 USC § 103(a) as allegedly being unpatentable over Coffin et al. WO 99/38955 as applied to claims 1, 2, 4, 7-16, 32-34, 60 and 61 and further in view of Herlitschka et al. (US 6,114,146). The Examiner contends that Coffin et al. teaches an HSV virus incorporating a nucleic acid encoding NTR, a nucleic acid encoding a ribosome binding site, and a marker, with the nucleic acid encoding NTR upstream of the ribosome binding site which is upstream of the marker. The Examiner states that Coffin et al. does not teach use of a ribosome binding site, arrangement of cassette and use of SV40 polyadenylation signal. The Examiner states that Herlitschka et al. teaches inclusion of a ribosome binding site between the foreign gene and the marker gene. The Examiner states that there would have been a reasonable expectation of success in using an expression cassette as taught by Herlitschka et al. in the manner taught by Coffin et al, and thus the invention was *prima facie* obvious.

It is respectfully submitted that in view of the amendments to independent claim 1, from which the cited claims 17-26 depend, a *prima facie* case of obviousness does not exist for claims 17-26. Specifically, the amendments to claim 1, in particular the amendment limiting the HSV species to those that are oncolytic, provide an element of the instant claims that was not disclosed in the cited references, as discussed in Applicants' arguments against the Examiner's 35 U.S.C. 102(b) rejection and referenced herein. Briefly, it is submitted that there is no teaching in WO 99/38955 that the innate lytic ability of HSV may exploited to kill tumour cells. On the contrary, WO 99/38955 explicitly teaches that HSV mutants should not lyse cells (page 1, lines 16-18). Clearly, there is no teaching in WO 99/38955 that would have prompted the skilled person to provide HSV comprising an NTR gene that is capable of lysing cells. Therefore the herpes simplex viruses of the claims would not be obvious to the person skilled in the art over WO 99/38955. In view of the amendments to the claims Applicants submits that the rejection should be withdrawn.

Aside from the lack of the "lytic" element in claim 1, Applicants also note that an oncolytic HSV which encodes NTR, and does not produce a functional ICP34.5 gene product, have a synergistic effect in killing tumour cells both *in vivo* and *in vitro* (see page 84, lines 1 to 21 and Figure 31) when used together with a prodrug that is susceptible to NTR cleavage. It is submitted that such synergistic effect was neither expected nor predictable. The skilled person would not know or expect whether an HSV with all of the elements as instantly claimed would (i) effectively express the nitroreductase *in vivo* and if it did, (ii) whether it would do so in sufficient quantity or for long enough (prior to oncolysis of the cell by the virus) for it to convert prodrug resulting in a cell killing effect over and above that mediated by viral oncolysis.

Essentially, it is submitted that the lysis of the cells by the virus makes it unpredictable to the skilled artisan whether the NTR could be synthesized in adequate amounts and made available in the cells for prodrug conversion. The skilled person would expect that the ongoing lysis of the cells by the HSV renders the duration and amount of NTR polypeptide expression in the cells uncertain. Surprisingly, it was demonstrated by Applicants that HSV1790 managed to express the NTR in a functional manner allowing for sufficient expression of nitroreductase to potentiate prodrug conversion. Further, the concurrent oncolysis of the cells by the virus was demonstrated not to negate the ability of the cells to express nitroreductase or the ability of the nitroreductase to convert the prodrug. See page 82, lines 23-27, teaching that treatment with HSV 1790 (encoding the NTR) and prodrug resulted in a significant reduction in tumor growth. The data on page 85, lines 1-11 indicate that enough NTR was expressed that, even following lysis of the cells in which it was produced, a "bystander" effect was present.

Applicants respectfully submit that the unpredictability of the combination of the elements, e.g., a lytic virus together with required NTR expression, provides rebuttal evidence against the Examiner's alleged *prima facie* case of obviousness (n.b. the existence of such alleged *prima facie* case is not accepted by Applicants).

Reconsideration is respectfully requested.

Claims 36, 37, 42, and 62-64

The Examiner has rejected claims 36, 37, 42 and 62-64 under 35 U.S.C. § 103(a) as being unpatentable over Coffin et al. as applied to claims 1, 2, 4, 7-16, 32-34, 60 and 61 above, and further in view of Anlezark et al. (WO 108288). The Examiner contends that the claims are drawn to a composition or kit comprising HSV and an NTR prodrug such as CB1954. The

Examiner contends that it would have been obvious to combine the constructs of Coffin et al., which encode NTR, with a prodrug such as CB1954 as taught by Anlezark et al.

Similar to the arguments used above for the obviousness rejection for the claims dependent from claim 1, it is respectfully submitted that in view of the amendments to independent claim 34, from which rejected claims 36, 37, 42 and 62-64 depend, a *prima facie* case of obviousness does not exist for claims 36, 37, 42 and 62-64.

Specifically, the amendments to claim 34, in particular the amendment limiting the HSV species to those that are oncolytic, provide an element of the instant claims that was not disclosed in the cited references, as discussed in Applicants' arguments against the Examiner's 35 U.S.C. 102(b) rejection and referenced herein. Briefly, it is submitted that there is no teaching in Coffin et al. that the innate lytic ability of HSV may exploited to kill tumour cells. On the contrary, Coffin et al. explicitly teaches that HSV mutants should not lyse cells (page 1, lines 16-18). Clearly, there is no teaching in Coffin et al. that would have prompted the skilled person to provide HSV comprising an NTR gene that is capable of lysing cells. Therefore the herpes simplex viruses of the claims would not be obvious to the person skilled in the art over WO 99/38955. In view of the amendments to the claims Applicants submits that the rejection should be withdrawn.

Reconsideration is respectfully requested.

Allowable subject matter

Applicants thank the Examiner for noting the allowability of objected-to claim 3. The Applicants believe that in view of the amendments to base claim 1, base claim 1 should now be allowable. Applicants also wish to point out that claim 57 has no prior art rejections in the last Office Action and believe that the Examiner's rejection for claim 57 has been addressed fully in this Response.

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

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